

Endovascular treatment of ischemic stroke

Status and potential development

A literature review

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Abstract

The treatment for acute ischemic stroke is a delicate matter, especially since time relapse from ictus to treatment is of vital importance for the outcome. The constantly evolving treatment options aim towards achieving high revascularization rates and limit the time in order to prevent irreversible damage to the brain tissue. Although becoming more clear, predictors of positive outcome and selection of patients to receive endovascular treatment remains unproven. Promising results are seen when selection is based on imaging to determine still viable tissue and the localization of the occlusion. Furthermore it is known that revascularization is associated with improved outcomes, however it is still unclear which method, if any, is ideal and might be proven superior against the presently preferred medical treatment. The main goal of this review is to discuss available therapies for acute ischemic stroke and criteria that will help identifying patients who might benefit from them. In order to find selection criteria and decide whether endovascular treatment is superior to medical more randomized controlled studies are needed.

Abbreviations

ASPECTS: Alberta Stroke Program early CT Score. A 10-point quantitative topographic CT scan score used to detect early stroke changes on a CT-scan.

NIHSS: National institute of health stroke scale. Tool used to objectively quantify the impairment caused by a stroke.

CT-caput: Computed tomography of the head used in stroke treatment to diagnose and differ between intracranial bleeding and ischemic strokes.

NCCT: Non-contrast computerized tomography

MRI: A medical imaging technique used in radiology to investigate. MRI scanners use strong magnetic fields and radio waves to form images of the body.

ICA: Internal Carotid Artery

MCA: Middle Cerebral Artery

ACA: Anterior Cerebral Artery

VBA: Vertebrobasiliar artery

IVT: Intravenous Thrombolysis used to dissolve occlusions with the use of recombinant tissue Plasminogen Activator (rtPA) administered systemically.

IAT: Intra-arterial Thrombolysis. This delivery technique permits high concentrations of a lytic agent to be applied locally to the occlusion while minimizing systemic exposure.

Endovascular therapy: Therapy performed from the inside of a vessel via a catheter.

Modified ranking scale (mRS): commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke.

Penumbra: The area surrounding an ischemic event such as an ischemic, thrombotic or embolic stroke that is not efficiently perfused but is still vital. An area that may still be salvaged by treatment.

TIMI/TICI: Thrombolysis in Myocardial Infarction/Cerebral infarction. A scale used to measure blood flow after recanalization of an occluded vessel.

Introduction

The first description of stroke dates back to the days of Hippocrates. He described episodes of convulsions, impaired speech and paralysis in patients. Because the onset was so sudden he called it “apoplexy” meaning “struck with violence” in Greek (1).

Great advances were made when English physician Thomas Willis described the intracranial arteries, especially the ones known as the Circle of Willis. Later, during the nineteenth century R.L.K Virchow was the first who postulated that stroke was the cause of ruptured vessels or thromboembolic events. To describe the downstream loss of perfusion, Virchow established the term “ischemia”. The same century Charles Foix traced the deep and superficial arteries and correlated them to clinical signs. Ever since Charles Foix and his contribution to the studies of stroke, the knowledge and treatment of it has grown exponentially. New techniques in diagnostics, imaging and treatment of ischemic stroke is constantly evolving (1). The handling of patients undergoing diagnostics for ischemic stroke is a delicate matter. However, it is still not defined what selection criteria to use when deciding on treatment options. Time from onset of symptoms is of the essence, but equally important is the localization of the thrombus. Identifying collateral circulation is important in evaluating outcome, as well as the primary therapeutic efforts.

Apart from this is the fact that there are now several different types of treatments. One usually divides them into medical and endovascular recanalization. Intravenously administered recombinant tissue plasminogen activator (rtPA) is the most commonly used treatment aiming towards dissolving the thrombus. In the other part of the spectrum is the endovascular mechanical recanalization of the thrombus. The latter one is used with the help from imaging done in interventional laboratories. Access to the occluded vessel is most commonly gained from introducing a guided wire through the femoral artery. The wire is then guided up to the intracranial occluded vessel where it is used to open it mechanically with or without the administration of actilyse. More studies now point in the direction that interventional recanalization might be the preferred treatment in occlusions presenting in large intracranial arteries. Patients with occlusions in the major cerebral arteries experience the most severe impairments such as reduced daily function, speech and paralysis.

Stroke is the third most common cause of death in Norway and the most common cause of long-term impairment of daily function and treatment. It is stated that a great proportion of reduced function in the people who experience a stroke can be prevented if fast ways in diagnosing and giving the patients efficient treatment were available.

During the last 10-20 years the management of ischemic stroke has changed tremendously. Earlier the only option was rehabilitation. Though rehabilitation still is a cornerstone in treating patients who experience a stroke, there are of course still much to be achieved regarding ideal stroke treatment in the future.

When diagnosing large intracranial occlusions prehospital skilled personnel are of high importance. In addition strategies of communication between the ambulance transporting the patient and specialized stroke units help reduce the time from onset of symptoms to adequate treatment. The hospital admitting the patient must have effective and standardized algorithms in order to not stall the initiation of treatment.

Methods for literature search

A literature search was performed in McMaster PLUS through “helsebiblioteket.no” using the terms “Endovascular AND ischemic stroke”. Other studies were found searching pubmed using the terms “acute ischemic stroke AND prognostic factors”, “endovascular treatment AND stroke” and “Stroke AND imaging”. Only articles in English and Norwegian were used.

Methods: What may improve flow?

IVT: Intravenous treatment

Administration of alteplase (a tissue plasminogen activator) is the standard treatment for acute ischemic stroke. It remains the only approved therapy by the FDA (the US food and drug administration). Alteplase administration is associated with good outcomes if it is given within 3 hours from onset of symptoms. In 1995 the NINDS study studied the difference in outcome when treating patients with ischemic stroke with alteplase vs. a placebo. The study showed superior results as compared to placebo, when the treatment was initiated within 3 hours after onset of symptoms. It was concluded that despite the increased incidence of haemorrhage improvement in clinical outcome at three months was found (2).

In the third international stroke trial (IST-3) carried out by Sandercock et al (3) the studies intention was to determine whether or not patients might benefit from IVT up to 6 hours after symptom onset. In this international, multicentre, randomised study it was concluded that despite the early hazards, thrombolysis within 6 hours improved final outcome. Furthermore it concluded that benefit was not reduced in patients who were older than 80 years. Still, the issue concerning intracranial haemorrhage (ICH) remained showing an increased incidence in the group treated with alteplase. However, according to the guidelines stated by the AHA/ASA (the American Heart Association/the American Stroke Association) the time period remains 3,5-4 hours from onset of symptoms. The ECASS III study confirmed that patients might benefit from IV rtPA from 3-4,5 hours (4). Multicenter trials performed between the one carried out by the NINDS study group and IST-3 have shown largely similar results in the time window from onset to treatment initiation (5). Seeing IVT is the most readily available method in achieving recanalization after an ischemic stroke it is still the most used treatment now.

Intra-arterial fibrinolysis.

This method uses a micro catheter placed into the proximity of the occluded artery. Once in place the operator infuses the fibrinolytic substance in order to dissolve the thrombus. There are two randomized trials that show support for the use of intra-arterial fibrinolysis: The PROACT II study and the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT). The PROACT II study was the first randomized multicenter trial sought to demonstrate efficacy of intra-arterial thrombolysis in patients with acute stroke caused by MCA occlusion (6). A total of 180 patients who presented less than 6 hours after symptom onset were randomized to receive either intra-arterial (IA) prourokinase (proUK) plus heparin or heparin alone. The outcome was measured and based on the proportion of patients with neurological disability at 90 days. The results stated that 40% of the proUK and 25% of the control patients had a modified ranking scale (mRS) of 2 or less at 90 days ($P=0.04$). Furthermore patients treated with proUK reached independence in activities of daily living

earlier although this was not of statistical significance at 90 days ($P=0.24$). Middle cerebral artery (MCA) recanalization was achieved in 66% of the r-pro-UK arm and 18% of the control group ($P<0.001$). Despite these positive results the fact remained that post-procedural haemorrhage was more frequent in the interventional group. Within 24 hours intracranial haemorrhage with neurological deterioration had occurred in 10% of the patients receiving proUK and 2% of the ones receiving heparin alone. However at 10 days the percentage of the ones experiencing intracranial haemorrhage in the intervention contra the control group was 68% and 57% respectively ($P=0.23$). The study concluded: “PROACT II has demonstrated that the therapeutic window for a significant number of patients with major stroke due to MCA occlusion may extend to at least 6 hours”. The issue remains finding the patients who might benefit from the treatment at that time point.

The MELT study carried out in Japan was a trial which randomized patients with occlusion in M1 or M2 presenting within 6 hours to either receive IAT (intra-arterial therapy) with urokinase or control (7). It was discontinued prematurely because of the approval of intravenous infusion of tissue plasminogen activator in Japan. Before the discontinuation of the study it had showed positive results, however, not reaching statistical significance it was concluded that the analyses showed that intra-arterial fibrinolysis has a potential to increase functional outcome.

Although lack of evidence intra-arterial approach is thought to be more effective for treatment of the more proximal arterial occlusions as compared to the intravenous treatment. A NIHSS over 10 and imaging pointing towards the occlusion of a major intracranial artery indicates a potential for good outcome when treating a patient with intra-arterial thrombolysis. Although the studies carried out so far show promising results there are still missing data in order to prove its superiority vs. intravenous rtPA (5).

Bridging.

It is understandable that when treating ischemic strokes with endovascular methods a delay to initiation of therapy is inevitable. Furthermore, it has been seen that rtPA alone has a lesser chance of achieving recanalization in the event of occlusions in more proximal arteries (8). Therefore, it has been proposed that treating strokes with administration of rtPA before intra-arterial fibrinolysis might help in raising the efficacy. The Interventional Management of stroke (IMS) II Study showed promising results (9). It was a multicenter study that screened patients at 13 clinical sites in North America. The subjects included in the study were first treated with IV rtPA. The ones that had arterial occlusion at angiography received additional rtPA through a micro-infusion catheter at the site of the thrombus. In the discussion it was stated that the patients who participated in the IMS II study were significantly more likely to have an excellent outcome at three months. This compared to the individuals who had participated in the NINDS rtPA Stroke trial mentioned above.

Because of the results presented in the IMS II study the IMS III study was initiated in 2006 (10). The goal was to enrol 900 subjects with a NIHSS of 10 or more. The ones randomized into the intervention group after receiving IV-rtPA were supposed to receive further treatment with either the EKOS Micro-Infusion, MERCI thrombus-removal device, the Penumbra System, the Solitaire FR device or infusion via a standard micro catheter. Those were the aims presented. The study was stopped early due to futility after 656 patients had undergone randomization. The proportion of patients with a mRS of 2 or less after 90 days did not differ between the intervention and control group. The study further highlighted that improved revascularization after the procedure was not a guarantee of clinical efficacy as compared to IVT alone. In the study, due to early stop, only a few patients were treated with

stent retrievers (a newer generation thrombectomy device). It concluded that the efficacy of the new devices as compared with IV rtPA alone remains to be demonstrated.

Another study presented in Radiology in 2013 performed by Roubec et al. showed more promising results (11). The purpose of their study was to compare the safety and utility of intra-arterial revascularization with stents to no mechanical revascularization in patients who failed to respond to IVT or had contraindications to it. Group 2A and 2B comprised of the patients who had IVT failure and received intravascular therapy or no further treatment respectively. There was a significant difference in favourable outcome at 3 months being 43.5% in 2A and 15.4% in 2B ($P=0.03$) indicating the potential in combining the use of IVT and endovascular therapy.

MERCI

The Merci retriever was the first device used for mechanical extraction of a thrombus. The device consists of a long wire with a helical coil formed at the end. When the retriever goes through the thrombus the coil reforms around the clot allowing it to be pulled back through the catheter. In the MERCI trial published in Stroke 2005 the results were promising (12). In this nonrandomized multicenter trial patients were treated with the device if they presented within 8 hours after stroke onset. Recanalization was seen in 48% of the patients in whom the device was used. Furthermore, a mRS at or below 2 was seen more frequently in patients who experienced recanalization as compared to those who did not (46% versus 10%, $P<0.0001$). Not only was the study showing positive results as regards to recanalization and low numbers of mRS, more importantly, it concluded that it was possible to reopen occluded vessels within 8 hours after symptom onset and that it actually was a safe alternative when contraindications towards thrombolytics existed. Compared to the NINDS, IMS trial and PROACT-II study it also had less frequent complications in forms of haemorrhage.

Three years later came the results from the Multi MERCI trial (13). This was an international, multi centre, prospective study in which patients who had received IV rtPA but still had large vessel occlusion was included. In this study a newer generation device was used, however not reaching the point of statistical significance in recanalization as compared to the older generation. The study was indeed important as it further supported the correlation between the degree of recanalization and good clinical outcome. This was not a controlled study so it was unable to prove that thrombectomy improves stroke outcomes.

PENUMBRA

The Penumbra stroke system consists of an aspiration pump, reperfusion catheters and separators. By placing a reperfusion catheter at the proximal end of the thrombus and connecting it to a vacuum pump, aspiration of the thrombus is made possible. By advancing and withdrawing the separator the goal is to debulk the thrombus into smaller pieces while keeping a steady suction to achieve recanalization. The Penumbra pivotal trial sought to see whether or not the Penumbra System was safe and effective in reducing clot burden in patients with large vessel occlusions (14). Revascularization occurred in 81.6% of the patients. Lower numbers of ICH were reported as well. Twenty-five percent had either a NIHSS score of 0-1 or a 10-point improvement at discharge. The same percentage was seen in the patient group with a mRS under 2 at 90 days. This was comparable to the MERCI trial but lower than the PROACT II study. This was unexpected seeing that a high amount of patients experienced successful revascularization. According to the authors the reason for this remains unclear. They do, however, state that the possibility of the Penumbra System not improving the patients activities of daily living at 90 days seems unlikely because analysis of

open versus closed vessels in the study showed a benefit in all measures in neurological and functional status, including mortality. Another possibility, they continue, might be the small number of patients included in the study. The study proved that the Penumbra system was indeed a safe and effective as regards to revascularization in patients with ischemic stroke treated within 8 hours. However, this was not a controlled trial. In order to prove the Penumbra Systems superiority over IV-rtPA in post procedure neurological recovery, controlled trials will be the deciding factor.

One year later a retrospective case of 157 patients from seven international centres was performed (15). The results showed even higher numbers of revascularization and 41% of the patients included had a mRS at or below 2. No major difference between the groups studied in the pivotal and post study was indentified. The differences in the results as regards to mRS at 90 days remain unclear.

Stent Retrievers

This is a newer generation device for thrombectomy. The access to the occluded vessel is through the femoral artery. The catheter is guided to the occluded vessel and then used to penetrate it. As the catheter is pulled back the stent is deployed and traps the thrombus in order to retrieve it.

There is one international, multicenter, prospective, single arm study published in 2013 that tested the Solitaire system (16). It included 202 patients from 14 stroke centres across Europe, Canada and Australia. Only patients with occlusions in the anterior circulation were enrolled. The study showed that the Solitaire Flow Restoration device achieved successful revascularization in patients with anterior occlusion as well as low numbers of ICH and mortality. The low mortality at 90 days being 6.9% was hypothesized to be correlated to the imaging based patient selection limited to anterior circulation strokes. mRS at 90 days at or below 2 was 57.9%. As this was not a randomized controlled study it concluded that the positive results supported further investigation in randomized controlled trials against medical treatment alone.

The TREVO device is another stent retriever that works in a similar way as the Solitaire device. A study published in 2013 provided data that the TREVO system was a safe and effective alternative for patients who had a stroke and were treated within 8 hours (17). Among the 60 patients who were enrolled the recanalization rate was 91.7% (thrombolysis in cerebral infarction (TICI) score at or above 2a) and a 90 day mRS at or below 2 was seen in 55%. Again promising numbers were presented. However, as in preceding studies, randomized controlled studies comparing stent retrievers against medical treatment are necessary to determine their superiority.

Comparing endovascular treatments.

Presently there are two major studies that have compared different endovascular treatments against one another. Those are the SWIFT and TREVO 2 study. The SWIFT study was a randomized, parallel study that enrolled patients to either receive treatment with the Merci- or Solitaire device (18). The results presented in Lancet in 2012 showed significant better results pointing towards the Solitaire device. Recanalization without symptomatic ICH was seen in 61% with the Solitaire- and 24% with the MERCI device. Further, mRS at 90 days was more favourable in patients treated with the Solitaire device. This study was halted early as the pre-specified criteria when to stop the study were met. This was an important study as it was the first one comparing two revascularization devices.

The second one, the TREVO 2 study compared the TREVO and the MERCI device (19). Again the MERCI one fell short against a stent retriever. In this study patients at 26 different sites were enrolled. The patients were randomized to receive treatment with either the MERCI or TREVO device. The study showed that revascularization was accomplished more often in the TREVO group. The mRS at 90 days at 2 or below was 40% in the TREVO group and 21.8% in the MERCI group. These two studies show that the stent retrievers are in fact superior in means of revascularization of occluded vessels as well as accomplishing better independence 90 days after an acute ischemic stroke.

Predictors of positive outcome

One of the most essential foundations in stroke therapy is rapid clearance of a thrombus to restore blood flow in the occluded vessel. The term “time is brain” was therefore introduced meaning that for every minute a vessel remains occluded tremendous amounts of neurons dies. However, selection criteria for whom to treat in terms of endovascular therapy contra intravenous have not been well postulated.

Role of imaging

Imaging will always have an important role in the treatment of acute ischemic stroke. CT of the brain is one of the cornerstones seeing that there are no other certain ways of differentiating between stroke due to occlusion or haemorrhage. Ordinary CT of the brain has a low sensitivity in showing early changes in infarction and not fit for selecting patients who are most likely to benefit from endovascular thrombectomy. On the other hand CT or MRI with perfusion-weighted sequences are able to identify the penumbra. This is the brain volume surrounding the infarct core with reduced perfusion but may still be salvaged if blood flow is normalized. Due to this the DEFUSE 2 study published in Lancet 2012 sought to establish whether a MRI could identify patients who would benefit from endovascular therapy (20). The results were positive and showed that target mismatch, mismatch between the infarct core and hypoperfused area, in patients prior to successful reperfusion had better clinical outcome in terms of reduced mRS at 90 days. The authors concluded that a randomized controlled study with patients eligible for endovascular therapy with a mismatch on imaging would be necessary. Unfortunately a second study presented in the New England Journal of Medicine in 2013 did not show any superiority in outcome when this was done (21). This was a randomized trial in which patients with anterior circulation occlusions were assigned to either mechanical thrombectomy (Merci retriever or Penumbra system) or standard care (rtPA) within 8 hours after stroke onset. Before initiating treatment the patients underwent a CT scan or MRI in order to see whether or not the patients had a mismatch pattern or not. The results not only failed to show that patients with a mismatch pattern on neuroimaging would benefit from endovascular therapy, additionally endovascular treatment did not show any superiority against standard medical treatment. The authors state that the study highlight questions, one being the low recanalization rate in the embolectomy group. This might be due to the fact that only first generation devices were used although the newer stent retrievers have proven more effective in accomplishing fast recanalization. Moreover, this study had a longer time to treatment than the DEFUSE 2 trial, again highlighting the importance of early recanalization. In 1998 a study was initiated that aimed to study whether intra-arterial or intravenous thrombolysis would be more effective for patients with a hyperdense middle cerebral artery sign (HMCAS) on CT (22). In this observational study the patients receiving intra-arterial thrombolysis were proven to benefit more than the ones

receiving intravenous if they presented with a hyperdense MCA sign. Another study published in Stroke hypothesized that the final stroke volume was in fact the true image predictor in patients who underwent endovascular therapy (23). The authors identified patients with an anterior circulation stroke who had undergone final infarct imaging. The results showed correlation between the final infarcted volume and mRS at 3 months. They concluded that a smaller final infarct volume is the best predictor of 3-month functional independence. The presently ongoing DAWN trial is a retrospective multicenter study enrolling patients who were last seen well 8 hours or more before having a confirmed occlusion in an anterior circulation proximal vessel by angiography (24). The preliminary results are indicating that endovascular treatment can safely be used after 8 hours as long as selection is based on perfusion imaging.

Seeing that CT has to be done before IV therapy can commence it has been speculated in ways to predict outcome in stroke treatment. One of these non-contrast CT (NCCT) methods used for evaluating early parenchymal injuries is the Alberta Stroke Programme Early CT Score (ASPECTS) (25). The scoring system comprises 10 regions in the MCA perfusion territory. One point reduction is counted if one territory of the ten appears to be affected by ischemia. Studies have shown that an ASPECTS score at or above 7 predicts good clinical outcome after endovascular treatment (26).

Selection of patients and techniques

According to studies the effect of rtPA reduces with time and more proximal occlusions. Furthermore, the risk of re-occlusion enhances with time. Recanalization rate of the middle cerebral artery and the internal carotid artery is said to be as low as 25% and 10% respectively when using alteplase (27). In addition the fact that patients may respond differently to IV-rtPA have resulted in the search for different ways of opening occluded vessels. In order to select patients who are eligible for treatment one must first identify what may predict good clinical outcome.

In a study published in 2012 the authors prospectively acquired data from patients who had infarcts in the carotid artery territory (the carotid, the middle and the anterior cerebral artery) who received endovascular therapy (28). The study continued between 1992 and 2010 when the endovascular treatment had evolved substantially. On admission NIHSS was scored and other clinical data was gathered. CT or MRI was performed in order to localize the occlusion as well as classify collateral vessels. Clinical outcome was registered at 3 months. The study concluded that a next day post recanalization improvement in NIHSS was associated with improved outcome and survival at 3 months. Furthermore, when more variables were analysed good collaterals, successful recanalization and hypercholesterolemia proved to be the strongest predictors for survival. The location of the occluded vessel also predicted outcome (see later). Good outcome at 3 months (mRS at or below 2) was predicted by better recanalization, hypercholesterolemia, lower NIHSS on admission, young age, absence of diabetes and good collaterals. Surprisingly, time from onset of symptoms did not predict outcome when collaterals was included in the multivariate model, only when it was excluded. This suggests that collaterals have a major role to play in the selection of patients available for endovascular therapy. This has been proven in other studies as well (29). Although this was a single centre non-blinded study it suggests that collaterals play a crucial part for the longer treatment window expected when compared to IVT. In the trial the majority of patients had occlusions in the internal carotid artery and the MCA. These have more collateral channels than the peripheral ones. Seeing that proximal occlusions have a higher chance of recanalization than distal ones, endovascular treatment might be especially promising in such cases.

The first systematic review correlating recanalization to clinical outcome was a meta-analysis performed by Rha et al (30). It included 53 studies with the total amount of 2066 patients. It confirmed the association between recanalization and outcome. The pooled analysis of the MERCI and Multi MERCI trials published in 2009 also concluded that final recanalization represents the strongest predictor of clinical outcome both in the univariate and multivariate analyses (31). mRS 0-2 was seen more frequently in patients who experienced a thrombolysis in myocardial infarction (TIMI) score of 2-3. Similarly, younger age and lower NIHSS were also strong positive predictors. Occlusions in the ICA demonstrated to be an independent predictor of mortality but do not decrease the chance of good outcomes after thrombectomy. There is still a debate surrounding whether or not blood pressure should be optimized during stroke treatment. On the one hand it has been postulated that a higher blood pressure might protect the brain by increasing perfusion pressure to the penumbral tissue. On the other hand it is hypothesized that an elevated pre-treatment systolic blood pressure is related to poorer collateral flow. The pooled analysis showed that hypertension has a negative impact on recanalization and suggest that a further understanding of physiology is needed before implementing management of blood pressure in guidelines.

Making the decision of therapy further complex, size of the occlusion also plays a part. Riedel et al. in 2011 hypothesized that the recanalization of occluded vessels depends on the length of the thrombus (32). In their study they included 138 patients who presented with acute MCA stroke and who were treated with rtPA. The clot size was measured in terms of length and depicted as arterial hyperdensities on nonenhanced CT. The study showed that IVT has very moderate chances of achieving recanalization in a thrombus exceeding 8 mm.

Localization

The localization of an occluded vessel is usually divided into the ones occurring in the anterior and the posterior circulation. The posterior circulation comprising the major arteries of the left and right vertebral arteries, the basilar artery and the two posterior cerebral arteries. The anterior circulation comprising the right and left internal carotid arteries and their branches, mainly the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). Untreated the localization of the occlusion has impact on mortality. Studies suggest that a complete MCA stroke has a mortality of 78% (33). Meanwhile for basilar occlusion 80% disability or death might be seen (34).

Posterior circulation

Ischemic strokes in the posterior circulation accounts for approximately 20% of the total amount. Despite the involvement in the treatment of acute ischemic strokes the results are not as applicable to patients with occlusions in the basilar artery. There are many reasons for this, the most prominent being the lesser amount of patients with occlusions in the posterior circulation and the fact that no studies have included only occlusions in the posterior circulation in randomized controlled trials (34). In the only multicenter study that was initiated to randomize patients to either intra-arterial urokinase or anticoagulation alone the recruitment was so poor that no conclusion in terms of safety and efficacy could be drawn (35). The BASICS study was a prospective observational study that assessed outcomes in treatment of occlusions in the basilar artery (34). Stroke severity was divided in mild to moderate and severe. The treatment was divided into antithrombotic treatment only, intravenous treatment and intra-arterial treatment. The study failed in showing any superiority

of intra-arterial treatment against intravenous but has resulted in the ongoing randomized controlled BASIC study (36). This study will enrol patients specifically with occlusions in the posterior circulation and randomize them into endovascular therapy or intravenous. Results are pending.

Another multicenter study, which enrolled 180 patients with acute vertebrobasilar occlusion, who were treated with intra-arterial fibrinolysis, evaluated outcome retrospectively (37). The result showed that recanalization, whether partial or complete was significantly associated with a positive outcome ($P=0.001$), however being more positive with complete recanalization. The success of recanalization was also associated with the volume of the thrombus, being less effective if the thrombus volume exceeded 300 microL. These results support the hypothesis presented earlier that the true goal of endovascular treatment should be early and effective recanalization and that it holds true for posterior circulation occlusions as well.

Anterior circulation

The study of 623 patients with anterior vessel occlusions who received endovascular therapy performed by Galimanis et al. presented the clinical outcome in specific vessels in the anterior circulation (28). 16.5% of the patients had occlusions in the internal carotid artery, 12% in the carotid T (intracranial carotid bifurcation occlusion with involvement of the A1 and M1 segments), 44.6% in the M1 segment of the middle cerebral artery, 16% in the M2 segment, 8.7% in the M3/4 segment and 1.3% in the anterior artery. Two or more vessels were occluded in 19.6%, the combination of proximal carotid artery and the middle cerebral artery being the most frequent. Interestingly enough the outcome was dependent of the occluded vessel. For instance proximal occlusions had better chances of recanalization than distal. Even more interesting is the paradox fact that these occlusions were the ones with the worst clinical outcome at 90 days. In the internal carotid artery recanalization was seen in 85.4% of the patients but only 37% of them had a mRS at or below 2 at 90 days. In the patients with carotid T occlusions 62.7% received successful recanalization, however, only 13.3% had a mRS at or below 2 after 90 days. According to the authors this is most likely because the carotid T occlusions cut off the circle of Willis, a very important channel for collateral circulation.

The localization is an important predictor of outcome not only because the limitations of reaching the thrombus but also because the specific vessel anatomy of the brain. As stated earlier collateral circulation has a tremendous role to play in the clinical outcome of treated patients after 90 days. The localization of the occlusion not only reduces blood flow distal to it but also inflicts on the way collateral blood flow appears. The infarct area is larger the more proximal the occlusion is. The worst outcome is seen in occlusions in carotid T occlusions (occlusions comprising the bifurcation on the most cranial part of the carotid artery) due to the limited supply to and from the other normal side through the circle of Willis. In one study the authors also describe cases where partially lysed occlusions in the carotid T have migrated distally and initiated occlusions in MCA and ACA. This hampers retrograde filling of the leptomeningeal collaterals and further reduce the clinical outcome (29). Since these more distal occlusions might be harder to reach it might indicate that a functional stroke centre need both treatment choices: Endovascular to achieve quick recanalization of proximal large occlusions and IV-therapy for opening distal occlusions that might reduce retrograde collateralization. The pooled analysis of the MERCI trial concluded that although ICA occlusions have increased rates of mortality they do not decrease the chances of good outcomes after thrombectomy (31).

Status in Norway

Norway is a very diverse country in terms of terrain. Furthermore it has a small and very scattered population. Seeing one of the most important predictors of good clinical outcome is early recanalization this postulates obstacles in the treatment of these patients. Every year approximately 15000 face a stroke in Norway. In the future this figure will continue to grow because of an older population. Patients experiencing an ischemic stroke is a very heterogeneous group and therefore the best treatment is an individual carefully planned one (38).

The organisation in stroke treatment is divided into primary and specialized stroke units. One can find several reasons why IV-therapy is the treatment of choice in several stroke units. It can be initiated minutes after a NCCT has ruled out haemorrhage and the administration of rtPA does not need to be handled by a physician with any specific training as opposed to endovascular treatment. However, as earlier stated, IV-treatment is proven inferior against endovascular therapy in accomplishing recanalization of larger more proximal occlusions (39). Additionally there are several contraindications that rule out treatment with rtPA thereby making some of these patients eligible for the endovascular option. Looking at stroke treatment today in Norway only a few patients get referred to the specialized stroke units to receive endovascular therapy, the exception being the primary stroke units in the proximity of the specialized ones (40). Present guidelines state that a stroke patient is to be transported to the closest primary stroke unit. Although this might help to reduce the time to initiation of IV-treatment it might also delay the initiation of adequate interventional treatment if this proves to be an eligible patient. The time lost might be substantial if a patient first is transported to one unit, only to be transported to a specialized one when the diagnostic criteria for endovascular treatment are fulfilled. The key element, one might propose, to efficiently finding patients to transport to the specialized units is early prehospital selection. Specially trained ambulance personnel who can contact the specialized units when in doubt could manage this. One proposition is to decentralise more of the decision making to earlier instances so that patients are transported to the right place at once. The establishment of dedicated mobile stroke teams is another option. These could be summoned to patients with more severe stroke symptoms and help in the decision making in whom to send to the specialized units. One study used a mobile stroke unit (MSU) equipped with a CT-scanner, point-of-care laboratory and telemedicine connection (41). It showed that the use of a MSU reduced the time from alarm to therapy decision significantly being 35 minutes in the interventional group and 76 minutes in the control group ($P=0.0001$).

The primary centres are capable of administering rtPA meanwhile the specialized ones handle the endovascular procedures. There are currently 4 specialized units in Norway. The management of stroke patients should be organized in a way making it possible to identify those eligible for endovascular therapy. If one looks at the information presented above there are in fact some indicators that may point in the direction of who may benefit from the therapy, one of them being imaging. Studies show that large proximal occlusions exceeding 8 mm in length have less probability in getting recanalized with the use of IV-rtPA only. In order to find these occlusions NCCT is not sufficient. The use of CT with the addition of a contrast agent must always be evaluated otherwise potential patients might be overlooked. Many primary stroke units have these imaging possibilities but there are still those who do not. Furthermore, some of the primary stroke units lack the advantage of having continuous communication with a radiologist part of the day. This is of utter importance when deciding between the different types of treatments (40). Since there are studies that show positive

results treating patients with prolonged symptoms over 8 hours, perfusion-CT and MRI should be included in the diagnosing of particular patients. This might be economically and administratively challenging, although, seeing stroke therapy is constantly evolving and literature is pointing towards the importance of adequate imaging in the diagnostics, a lot of primary stroke units will have to change their routines in the management in acute ischemic stroke in the not too distant future. This could be a cost benefit factor for the healthcare in Norway since the growing older population will need substantial more prolonged and expensive rehabilitation after having suffered from a stroke.

Norway has an excellent ambulance transport service with helicopters and airplanes. This sets the foundation for inclusion of a larger population who could be treated with endovascular therapy seeing there are fewer obstacles in transporting patients from remote areas to the more central hospitals. Since Norway has a small and scattered population keeping the specialized units enables a steady flow of patients receiving up to date care. This does not only help to raise the amount of procedures done but also keep education and skills at an adequate level (42).

Results and discussion

The treatment and the way we look at stroke treatment today have changed tremendously over the last 20 years ranging from IV-rtPA to mechanical endovascular thrombectomy devices. Since individual responses to IV alteplase are very heterogeneous, additional intra-arterial thrombolytic and mechanical endovascular treatment is used more frequently. Although these devices have been proven to be very efficient in terms of recanalization and outcome in the single arm studies, data from randomized clinical trials have failed in showing their superiority against intravenous therapy alone. So far there are three studies that have tried to prove that the endovascular option leads to a better outcome. These are the IMS III, MR RESCUE and the SYNTHESIS EXPANSION trials (10, 21, 43). Showing discouraging results these studies have been the aim of major criticism because of the methods used in the respective trials. Quershi et al. bring up several points, one being the low NIHSS score of several patients who were included (44). This might point towards a favourable outcome regardless of treatment. It is particularly the SYNTHESIS trial that failed in this seeing they did not have any pre-specified NIHSS score that would include or exclude patients in the study making the results hard to interpret. Additionally, although imaging is an important factor CT or MR angiography confirming arterial occlusion was not required in the the IMS III and SYNTHESIS trial. This might be a confounding factor since there are studies supporting the use of CT angiography for determining the patients who might benefit from intra-arterial thrombolysis. Another point presented in the studies is the low number of patients with an occlusion in the posterior circulation. In the MR RESCUE trial none were included. The mortality rate remains high in these occlusions when using IV alteplase pointing towards the potential beneficial use of endovascular therapy. Moreover, it is hypothesized that outcomes in the 3 studies would have been different if a larger population had received treatment at an earlier state and had been treated with the newer stent retrievers.

Summary

Summarizing the material in this critical analysis one might see that there are still unanswered questions. Many investigators, including myself do not feel certain that endovascular treatment is proven to be inferior or even equal to intravenous thrombolysis. Based on the selection criteria for inclusion in the studies so far they are still considered to be non standardized and even random at some points. However, the fact remains, endovascular

therapy have been proven to be inferior in several studies although they show promising results in the single arm ones. Applying the knowledge gained from the IMS III, SYNTHESIS EXPANSION and MR RESCUE to general practise is, in my opinion, a bit too early to do seeing that there are still grounds to be covered. More randomized studies with clear and well-formulated inclusion criteria are needed. The aim should be focused on finding solid proof that help selecting patients who can benefit from endovascular therapy seeing there is a big probability that more patients are eligible candidates. Clear-cut criteria and easy to understand algorithms in terms of whom to send forward should be standardized, being less complicated at earlier stages and reliant on more expertise and diagnostic tools at later ones. One model would be the possibility to decentralize decision making to ambulance personnel giving them the ability to find younger patients with a NIHSS score at or above 10 without any medical comorbidity. Patients with more severe symptoms could be transported to locations that have an on call radiologist or the option of performing a CT angiography. The aim would be finding patients with a proximal arterial occlusion, ASPECTS score above 7 or a hyperdense MCA sign in time for relevant treatment. Needless to say, the goal should be limited time from onset of symptoms to initiation of treatment. This holds true but should on the other hand not exclude patients from being evaluated from further diagnostics with CT- or MR-perfusion scans seeing there are studies supporting recanalization several hours after the 8 hour window that is now postulated. Accordingly, identifying patients with adequate collateral circulation is of crucial importance selecting patients for late starting therapy.

A lot of expectation is put into the use of stent retrievers that have proven superior to the earlier generation thrombectomy devices. However to prove their superiority against the present medical guidelines well organized randomized control studies with clear cut inclusion criteria are essential. Stroke treatment is still in its younger years and the full potential in terms of imaging and revascularization devices is yet to be seen.

Conclusion

After having reviewed a substantial amount of recent articles in the field, the following conclusion and recommendations can be drawn. Endovascular treatment in patients with acute ischemic stroke is shown to be a safe and efficient procedure and its aim should be to achieve a high recanalization rate keeping the time from onset of stroke symptoms to initiation of treatment to a minimum. Endovascular treatment can be used even up to 8 hours after start of symptoms but the time window might be even greater. Although there is still a discrepancy between successful recanalization and clinical outcome there are in fact predictors of positive and negative outcome suggesting whom to treat with the endovascular option. As of today goals should be focused on early identification of patients who might be eligible using adequate imaging techniques. To draw further conclusions whether or not endovascular therapy is superior to IVT large randomized controlled trials with clear inclusion criteria are needed.

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